Exhibit 7

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Opioids in chronic non-cancer pain: systematic review of efficacy and safety

Eija Kalso[a,*], Jayne E. Edwards[b], R. Andrew Moore[b], Henry J. McQuay[b]

[a]*Pain Clinic, Department of Anaesthesia and Intensive Care Medicine, Helsinki University Central Hospital, P.O. Box 340, FIN 00029 HUS, Finland*
[b]*Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Oxford Radcliffe Hospital, The Churchill, Headington, Oxford OX3 7LJ, UK*

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Abstract

Opioids are used increasingly for chronic non-cancer pain. Controversy exists about their effectiveness and safety with long-term use. We analysed available randomised, placebo-controlled trials of WHO step 3 opioids for efficacy and safety in chronic non-cancer pain. The Oxford Pain Relief Database (1950–1994) and Medline, EMBASE and the Cochrane Library were searched until September 2003. Inclusion criteria were randomised comparisons of WHO step 3 opioids with placebo in chronic non-cancer pain. Double-blind studies reporting on pain intensity outcomes using validated pain scales were included. Fifteen randomised placebo-controlled trials were included. Four investigations with 120 patients studied intravenous opioid testing. Eleven studies (1025 patients) compared oral opioids with placebo for four days to eight weeks. Six of the 15 included trials had an open label follow-up of 6–24 months. The mean decrease in pain intensity in most studies was at least 30% with opioids and was comparable in neuropathic and musculoskeletal pain. About 80% of patients experienced at least one adverse event, with constipation (41%), nausea (32%) and somnolence (29%) being most common. Only 44% of 388 patients on open label treatments were still on opioids after therapy for between 7 and 24 months. The short-term efficacy of opioids was good in both neuropathic and musculoskeletal pain conditions. However, only a minority of patients in these studies went on to long-term management with opioids. The small number of selected patients and the short follow-ups do not allow conclusions concerning problems such as tolerance and addiction.

Keywords: Opioid; Pain; Chronic; Non-malignant; Randomised controlled trial; Systematic review

1. Introduction

Opioids are advocated by WHO for the effective treatment of cancer pain (World Health Organisation, 1996). Their role in chronic non-cancer pain is more controversial. It has been argued that certain types of chronic pain, e.g. neuropathic pain, do not respond to opioids (Arnér and Meyerson, 1988). Concerns have been expressed about the safety of long-term opioid administration (Large and Schug, 1995) because of adverse effects (Abs et al., 2000), development of tolerance to the analgesic effect (Ballantyne and Mao, 2003), addiction, and drug diversion (Moulton, 2003). Guidelines for responsible use of opioids in chronic non-cancer pain (American Academy of Pain Medicine, 2001; Kalso et al., 2003; The Pain Society, 2004) reflect concern over these problems.

Several controlled trials have been published on the efficacy and safety of various WHO step 3 opioids in chronic non-cancer pain. We searched for and analysed available evidence of efficacy and safety in the randomised, placebo-controlled trials.

2. Methods

2.1. The search

Full reports of randomised controlled trials (RCTs) of WHO step 3 opioids fentanyl, hydromorphone, methadone,

* Corresponding author. Tel.: +358 9 4717 5885; fax: +358 9 4717 5641.
E-mail address: eija.kalso@helsinki.fi (E. Kalso).

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morphine, oxycodone (Heiskanen and Kalso, 1997), and oxymorphone were sought using broad free-text searches of Medline (1966 to September 2003), EMBASE (1980 to September 2003), Cochrane Library (on-line September 2003) and the Oxford Pain Relief Database (1950–1994) (Jadad et al., 1996a), without restriction of language. Reference lists of reports and reviews were also searched. Abstracts, review articles and unpublished reports were not considered. Authors were not contacted for original data.

2.2. Inclusion criteria and reporting

Inclusion criteria were randomised comparisons of oral, transdermal or intravenous WHO step 3 opioid with placebo in chronic non-cancer pain. Only double-blind studies with at least 10 adult patients completing each treatment arm, reporting on pain intensity outcomes using visual analogue scale (VAS), a 0–10 numerical rating scale (NRS), or a 4-point pain intensity categorical scale were included. Inclusion was based on a consensus of all reviewers.

QUOROM guidelines for reporting meta-analyses were followed (Moher et al., 1999). Each report was scored for quality and validity using a three-item (1–5) quality scale (Jadad et al., 1996b) and a five-item (1–16) validity scale (Smith et al., 2000). The quality scale assesses the quality of randomisation, double-blinding and reporting on withdrawals and dropouts. The validity scale assesses blinding, size of trial groups, outcomes, baseline pain, internal sensitivity, and data analysis.

2.3. Data extraction

Information about the treatments and controls, numbers randomised and analysed, mean visual analogue scale for pain intensity (VASpi), verbal rating scale for pain intensity (VRSpi), numeric rating scale for pain intensity (NRSpi) and visual analogue scale for pain relief (VASpr), verbal rating scale for pain relief (VRSpr), adverse events and level of statistical significance was extracted.

Three periods were defined to evaluate effectiveness. First, effectiveness of treatment was assessed during intravenous (i.v.) infusions lasting up to 5 h. Second, effectiveness of oral or transdermal treatment was assessed during a 1–8 week trial period. Third, long-term effectiveness was assessed during 3–18 months open label follow-up. For the primary outcome measure, pain intensity difference or pain relief, effectiveness was defined as a statistically significant difference (as reported in the original trials) between opioid and placebo.

Assessment of secondary outcomes (mood, functional status, quality of life) and dose response were performed if data were available. In these comparisons effectiveness was defined as a statistically significant difference between different doses of opioid, or between opioid and placebo. The predictive value of i.v. opioid for later effectiveness of respective oral or transdermal opioid was extracted.

2.4. Analysis

Relative risk was calculated with 95% confidence intervals using a fixed effects model (Morris and Gardner, 1995). Heterogeneity tests were not used (Gavaghan et al., 2000; Higgins et al., 2002) though homogeneity was examined visually (L'Abbé et al., 1987). Funnel plots (Sterne et al., 2000; Tang and Liu, 2000) were not used for detecting publication bias. The number needed to harm (NNH) with confidence intervals was calculated by the method of Cook and Sackett (1995) from the sum of all events and patients for treatment and placebo. Relative risk was considered to be statistically significant when the 95% confidence interval did not include 1. NNH was calculated only when the relative risk was statistically significant, and is reported with the 95% confidence interval.

3. Results

3.1. Included studies

Eighteen randomised, double-blind, placebo-controlled trials met inclusion criteria. Two excluded studies (Kupers et al., 1991; Moran, 1991) had fewer than 10 patients per treatment arm. One study (Lacouture et al., 1996) was a duplicate publication of Roth et al. (2000).

Four studies tested intravenous opioid (Table S1, Fig. 1), three with morphine and one fentanyl. One included an open label follow-up of oral morphine (Attal et al., 2002) while another published an open label follow-up of transdermal fentanyl separately (Dellemijn et al., 1998).

Eleven studies compared oral opioids with placebo for periods ranging from 4 days to 8 weeks (Table 1, Table S1). Six used crossover designs and five parallel groups (Table 1). One trial (Raja et al., 2002) had three treatment arms, the third being an antidepressant. Five studies were of morphine, one of morphine or methadone, and four of oxycodone (Table 1). Six had an open label follow-up (Table 1), but only three reported the results (Caldwell et al., 2002; Huse et al., 2001; Roth et al., 2000). One study had initial randomised double-blind i.v. testing before oral dosing (Huse et al., 2001) but results were not reported.

Two studies (Moulin et al., 1996; Watson et al., 2003) used an active placebo (benztropine), all others using inactive placebo. Five studies (Attal et al., 2002; Huse et al., 2001; Maier et al., 2002; Moulin et al., 1996; Watson et al., 2003) tested concealment of blinding. The majority of both patients and investigators distinguished the opioid from both active and inactive placebo. One report studied dose response (Roth et al., 2000).

3.2. Quality and validity

Studies scored highly for both quality (mean 4, range 3–5) and validity (mean 14, range 10–18). The following

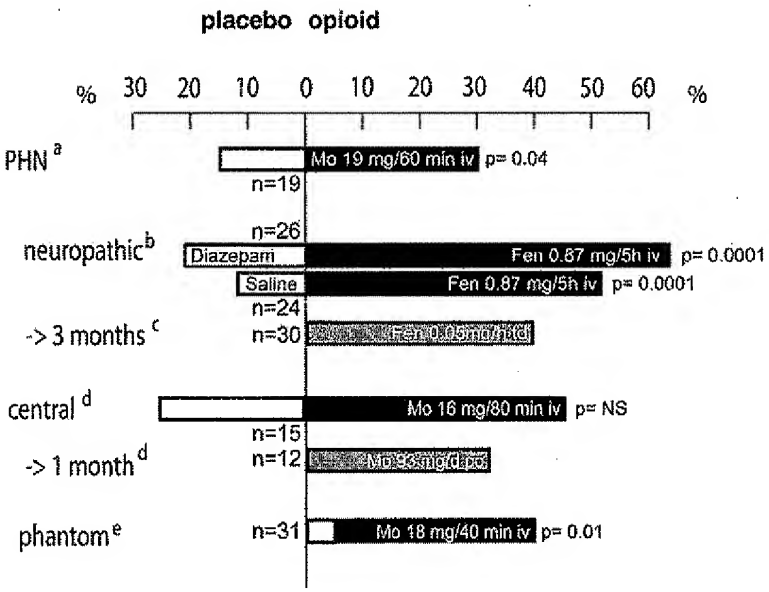

Fig. 1. Pain relief after intravenous opioid testing. The mean maximum % decrease in pain intensity is shown following the intravenous (i.v.) administration of morphine (Mo) or fentanyl (Fen) in neuropathic pain. The left-hand bar indicates the response after placebo and the right-hand bar the effect after the opioid. Dellemijn and Vanneste (1997) had two i.v. groups with different placebo-groups (diazepam or saline). Pain was increased during placebo treatment in the study by Wu et al. (2002). The number of patients is indicated with *n*. The pain condition is given on the left. The dose and duration of the infusions are given in the right hand bars. The level of statistical significance is given on the right. All i.v. studies used a crossover design. The results for an open-label follow-up study with transdermal (td) fentanyl (Dellemijn et al., 1998) and oral morphine (po) (Attal et al., 2002) are also shown. References: [a]Rowbotham et al. (1991); [b]Dellemijn and Vanneste (1997); [c]Dellemijn et al. (1998); [d]Attal et al. (2002); [e]Wu et al. (2002).

problems were found: opioid response was weaker when given after placebo (Maier et al., 2002; Moulin et al., 1996), concealment was not maintained (Huse et al., 2001; Maier et al., 2002; Moulin et al., 1996; Watson et al., 2003) or it was likely not maintained as opioid titration preceded the actual study (Caldwell et al., 1999). Only 6 of the 14 studies had performed a power calculation (Caldwell et al., 1999; Gimbel et al., 2003; Moulin et al., 1996; Raja et al., 2002; Watson and Babul, 1998; Wu et al., 2002).

3.3. Patients

Duration of pain before allocation was more than 1 year in one study, over 6 months in three studies and over 3 months in five (Table S1). The remaining six studies did not define duration of pain as an inclusion criterion. Baseline pain intensity was always at least moderate (above 30–40% of the maximum possible).

In one study, no patient had previously been on opioids whereas seven had an average of 49% of patients previously

Table 1
Design of studies using oral opioid dosing

Reference	Condition	Design	Opioid	Duration per treatment arm	Open label follow-up
Caldwell et al. (1999)	Osteoarthritis	Parallel group	Oxycodone, mean 40 mg/day	4 weeks	No
Caldwell et al. (2002)	Osteoarthritis	Parallel group	Morphine, 30 mg/day	4 weeks	Yes
Gimbel et al. (2003)	Diabetic neuropathy	Parallel group	Oxycodone, 42±27 mg/day	4 weeks	No
Harke et al. (2001)	Peripheral neuropathic pain	Parallel group	Morphine, mean 83 mg/day (range 60–90)	8 days	Yes
Huse et al. (2001)	Phantom limb pain	Crossover	Morphine, mean 120 mg/day (range 70–300)	4 weeks	Yes
Maier et al. (2002)	Mixed types of pain	Crossover	Morphine, mean 114 mg/day (range 60–180)	4 days	No
Moulin et al. (1996)	Musculoskeletal pain	Crossover	Morphine, mean 83.5 mg (range 60–130)	6 weeks	No
Raja et al. (2002)	Postherpetic neuralgia	Crossover	Morphine, 91±49 mg/day; methadone, 15±2 mg/day	8 weeks	No
Roth et al. (2000)	Osteoarthritis	Parallel group	Oxycodone, 20 mg/day or 40 mg/day	2 weeks	Yes
Watson and Babul (1998)	Postherpetic neuralgia	Crossover	Oxycodone, 45±17 mg/day	4 weeks	No
Watson et al. (2003)	Diabetic neuropathy	Crossover	Oxycodone, 40±28.5 mg/day	4 weeks	Yes

on opioids, usually codeine or oxycodone in a combination with paracetamol (Table S1). Three studies did not state whether the patients had previously been on opioids, and four reported that patients had previously received opioids but gave no proportion.

Psychological issues were described in six studies. In four patients were excluded if there was a significant psychiatric component (Table S1). Based on the Zung scale, all patients in one study (Dellemijn and Vanneste, 1997) were depressed, severely so in 44 out of 50. In 10 of 14 studies history of drug or alcohol abuse was an exclusion criterion (Table S1).

3.4. Intravenous opioid testing

All four trials were crossover studies in neuropathic pain (postherpetic neuralgia, mixed neuropathic pain, central pain and phantom pain) (Table S1). An initial 120 patients were randomised, with 115 completing.

Three studies titrated the infusion either to a target total dose (Rowbotham et al., 1991) or a maximum tolerated dose (Attal et al., 2002; Dellemijn and Vanneste, 1997) and one (Wu et al., 2002) used a fixed dose. Mean doses of i.v. morphine, 19, 16 and 0.25 mg/kg, were comparable, and though the mean total equianalgesic dose of i.v. fentanyl was higher (0.873 mg), it was given over 5 h.

Using either pain intensity difference or pain relief as the endpoint, all four i.v. studies reported average pain relief of 30–60% with opioid. With placebo, the response varied from an increase in pain by 5% to a decrease of 25% (Fig. 1). Fig. 1 shows consistency of opioid analgesic effect in different neuropathic pain states, despite differences in the opioid used, different doses, and small numbers of patients.

Two studies tested allodynia (Attal et al., 2002; Rowbotham et al., 1991) which was reduced by opioid but not lidocaine. Only one study reported pain unpleasantness in addition to pain intensity. Both outcomes were equally reduced by opioid (Dellemijn and Vanneste, 1997).

Adverse events occurred in most patients (Table S2). A mean dose of 19 mg of morphine infused over 1 h caused vomiting in 37% (Rowbotham et al., 1991). With fentanyl (Dellemijn and Vanneste, 1997) 90% of infusions (5 μg/kg per h) were stopped before 5 h because of adverse events. Adverse events in an open titration to determine the maximum tolerated dose (Attal et al., 2002) prevented 14% of patients from participating in the double-blind phase. Of those who did participate, 60% experienced adverse events at the mean dose of 16 mg of morphine infused over 20 min. Wu et al. (2002) did not report any adverse events with morphine (0.25 mg/kg) infused over 40 min.

3.5. Oral opioid dosing

Eleven trials studied oral opioids for 4 days to 8 weeks (Table 1). Six were in neuropathic pain, four in musculoskeletal pain and one in mixed pain (Table 1, Fig. 2). Of 1025 patients randomised, 674 completed and 698 were evaluable. Adverse effects and lack of efficacy were the most frequent reasons for discontinuation during both opioid and placebo treatment (Table 2).

Seven studies had a double-blind titration lasting 3 days to 9 weeks (Table 1, Table S1). One had an open titration of 30 days (Caldwell et al., 1999). The maximum daily dose in the titration was 60–300 mg morphine, 120 mg oxycodone, and 80 mg methadone. The subsequent treatment period was from 4 days to 8 weeks, and mean final daily doses varied were 30–120 mg morphine, 20–45 mg oxycodone, and 15 mg methadone.

Fig. 2 summarises efficacy by study and details are shown in Table S2. Mean pain relief with opioid was about 30% in both neuropathic and nociceptive pain. In the two studies that looked at allodynia, mean weekly VAS for steady pain, brief pain and dynamic mechanical allodynia were significantly reduced with oxycodone compared with placebo (Watson and Babul, 1998; Watson et al., 2003).

All seven studies that assessed quality of sleep reported significant improvement during opioid treatment (Table S2). Two studies (Maier et al., 2002; Roth et al., 2000) noted improved sleep only in those with significant pain relief with opioid. Depression scores were not significantly improved in any of the six studies assessing it (Table S2). Mood was reported in two studies (Maier et al., 2002; Roth et al., 2000) where it was significantly improved in those patients with good pain relief with the opioid.

Five studies reported no significant difference during opioid or placebo treatments in either self-reported levels of overall activity or pain-related interference in daily activities (Gimbel et al., 2003; Raja et al., 2002), in pain disability index (Moulin et al., 1996), physical function (Caldwell et al., 2002; Gimbel et al., 2003) or interference by pain on walking ability or general activity (Gimbel et al., 2003; Roth et al., 2000). One study (Maier et al., 2002) claimed that significant improvement of pain-related disability was closely correlated with pain relief, and two (Watson and Babul, 1998; Watson et al., 2003) reported that the disability scores were lower during treatment with oxycodone compared with placebo.

Various aspects of quality of life were assessed in most studies. Only three used a validated quality of life questionnaire, the SF-36 (Gimbel et al., 2003; Watson et al., 2003) and the Sickness Impact Profile (Gimbel et al., 2003; Moulin et al., 1996). Only one (Watson et al., 2003) reported a positive difference in relation to most health-related quality of life domains of the SF-36 with oxycodone.

Table 2 shows results for all cause discontinuations, and discontinuations because of adverse events and lack of efficacy for oral opioids and placebo. There was no significant difference between opioids and placebo in all-cause discontinuation, because of a balance between more patients discontinuing with adverse events with opioids and more discontinuing with lack of efficacy with placebo.

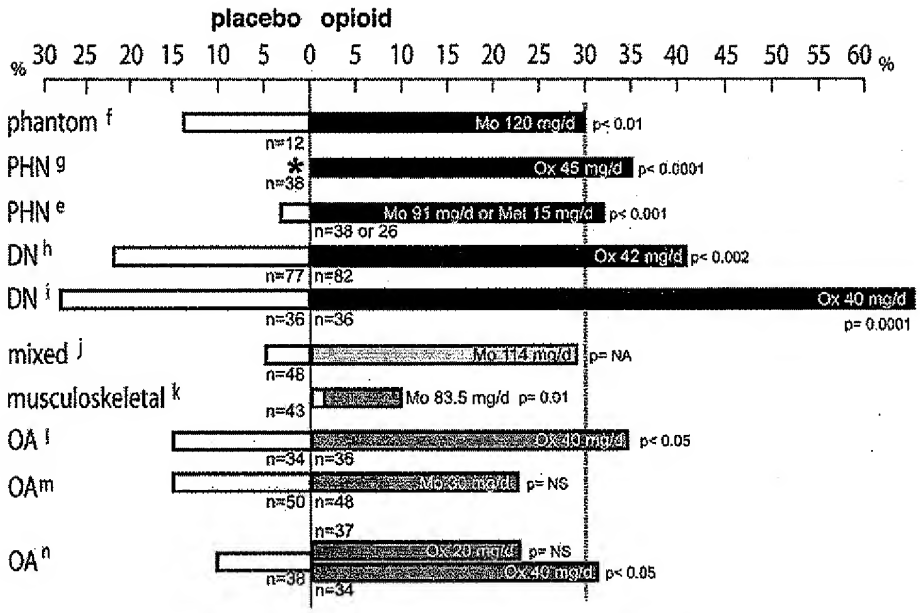

Fig. 2. The mean % pain intensity difference at the end of the treatment period is shown in the right-hand bars following oral administration of morphine (Mo), oxycodone (Ox) or methadone (Met) and in the left-hand bars after placebo. The number of patients in a treatment arm is indicated with *n*. The pain condition is indicated on the left. The black bars indicate neuropathic pain and the grey indicate musculoskeletal pain. The statistical significance and the duration of the study are shown on the right. In Moulin's study (1996) only the results of the first period are shown. The open bar indicates the mean increase in pain intensity with placebo. *The bar indicates a mean pain relief with oxycodone compared with placebo as the study did not report baseline pain intensities. The study by Raja et al. (2002) had three arms in the crossover design: placebo, an opioid (either morphine or methadone) or a tricyclic antidepressant (results not shown). All studies except those of Caldwell et al. (1999, 2002), Gimbel et al. (2003), and Roth et al. (2000) used a crossover design. It was not possible to extract data for pain intensity differences from Harke et al. (2001). The dotted line indicates the 30% decrease in pain intensity that has been suggested to represent the mean clinically important difference in pain relief in chronic pain (Farrar et al., 2000). References: [f]Huse et al. (2001); [g]Watson and Babul (1998); [h]Raja et al. (2002); [i]Gimbel et al. (2003), [j]Watson et al. (2003); [k]Maier et al. (2002); [l]Moulin et al. (1996); [m]Caldwell et al. (1999); [n]Caldwell et al. (2002).

With opioids, more patients (80%) reported having at least one adverse event than with placebo (56%). The number needed to harm was 4.2 (3.1–6.4), meaning that for every four patients treated with opioids, one more would have experienced an adverse event than if they were treated with placebo.

Specific adverse events were reported in most studies (Table S2). Constipation (41%), somnolence (29%), and nausea (32%) were most frequently reported with opioids, with vomiting (15%), dizziness (20%), and itching (15%) also reported significantly more frequently than with placebo. Differences between opioids and placebo were

Table 2
Discontinuations and adverse events with oral opioid

	Trials	Number/total (%)		Relative risk (95% CI)	NNH (95% CI)
		Opioid	Placebo		
Adverse event					
Discontinuation any cause	9	209/698 (30)	120/462 (26)	1.0 (0.8–1.2)	Not calculated
Discontinuation AE	8	159/677 (24)	67/445 (15)	1.4 (1.1–1.9)	12 (8.0–27)
Discontinuation LOE	6	55/558 (11)	68/326 (22)	0.4 (0.3–0.5)	−9 (−6.2 to −17)
Patient with ANY adverse event	4	181/225 (80)	124/220 (56)	1.4 (1.3–1.6)	4.2 (3.1–6.4)
Specific adverse events					
Constipation	8	275/673 (41)	50/441 (11)	3.6 (2.7–4.7)	3.4 (2.9–4.0)
Nausea	8	215/673 (32)	52/441 (12)	2.7 (2.1–3.6)	5.0 (4.0–6.4)
Somnolence/sedation	7	178/627 (29)	37/395 (10)	3.3 (2.4–4.5)	5.3 (4.3–7.0)
Vomiting	7	91/602 (15)	10/370 (3)	6.1 (3.3–11)	8.1 (6.4–11)
Dizziness	8	132/673 (20)	33/441 (7)	2.8 (2.0–4.0)	8.2 (6.3–12)
Itching	6	83/556 (15)	23/324 (7)	2.2 (1.4–3.3)	13 (8.4–27)
Dry mouth	7	76/585 (13)	37/396 (9)	1.5 (1.0–2.1)	Not calculated
Headache	4	35/437 (8)	28/240 (12)	0.8 (0.5–1.3)	Not calculated

NNH was calculated only when there was a significant difference from placebo, i.e. when the confidence interval of the relative risk did not include 1. A negative NNH becomes a number needed to treat, in this case to prevent lack of efficacy (LOE) discontinuation. AE = adverse event.

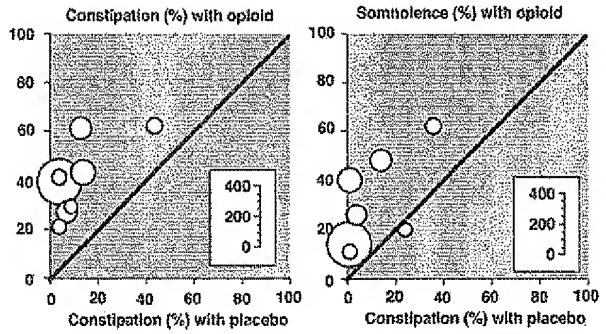

Fig. 3. Constipation and somnolence with oral opioids compared with placebo. Each symbol represents one study, and the size of the symbol reflects the size of the trial, according to the included scale.

consistent, and Fig. 3 shows the data from individual trials for constipation and somnolence. For constipation, the number needed to harm was lowest (worse) at 3.4 (2.9–4.0). This means that for every three patients treated with opioids, one more would be constipated than with placebo.

These results for adverse events were obtained in studies with a form of enriched enrolment. As an example, one study enrolled 167 patients into an original dose titration, but only 107 were eventually randomised (Caldwell et al., 1999). Dropouts before randomisation were mainly because of adverse events.

Six studies did not mention opioid withdrawal symptoms. Two studies reported that no signs of withdrawal were seen (Gimbel et al., 2003; Watson and Babul, 1998). One reported withdrawal symptoms after morphine in two patients (Maier et al., 2002), and another withdrawal in two patients after oxycodone (Roth et al., 2000). One study reported withdrawal symptoms in one patient when previous opioids were withdrawn and before entering the randomised study.

Seven studies did not mention addiction. Four patients (8.7%) reported drug craving with morphine and two with placebo (4.3%) in the study by Moulin et al. (1996). Maier et al. (2002) reported that no patient was diagnosed with drug abuse after 1 week on treatment, and Gimbel et al. (2003) stated that no aberrant drug-related behaviour was observed.

Two studies (Caldwell et al., 1999; Moulin et al., 1996) indicated that pain intensity levels started to rise after the 4-week titration period. One study (Gimbel et al., 2003) reported that no tolerance was observed. The remaining studies did not mention tolerance.

3.6. Open label follow-up studies

Eight of the 14 included trials had an open label follow-up, four of oral morphine, three of oral oxycodone and one of fentanyl (Table 1, Table S3). One (Gimbel et al., 2003) provided no data on the open label follow-up, and the results of another (Maier et al., 2002) are yet to be published.

At the end of the open label studies, between 7 months and 2 years, 44% of the 388 patients were still on opioids (Table S3). Adverse events were a common reason for discontinuation, as well as lack of efficacy, though no general conclusions could be drawn about their relative incidence.

No information about tolerance to the analgesic effect was given by three studies (Attal et al., 2002; Huse et al., 2001; Roth et al., 2000). One (Caldwell et al., 2002) stated, that "tolerance was not observed in the majority of patients", though most increased their dose of morphine during the follow-up. Another (Dellemijn et al., 1998) suggested that no tolerance occurred over 3 months, though during the first year tolerance occurred in 6% since pain relief no longer outweighed adverse events. Clear tolerance had developed in one of nine patients remaining in the study for 2 years (out of the 48 who began). In a third study (Watson et al., 2003) out of 30 patients who continued in the 1 year follow-up four needed increased opioid doses.

Two studies did not mention addiction or withdrawal (Caldwell et al., 2002; Huse et al., 2001). There were no signs of addiction in three patients who continued for 1 year (Attal et al., 2002), and another study (Dellemijn et al., 1998) reported that no addictive behaviour was observed. Severe withdrawal symptoms occurred in two patients (Dellemijn et al., 1998; Roth et al., 2000) who abruptly stopped opioid treatment and in a third who stopped opioids before entry (Watson et al., 2003). Roth et al. (2000) reported that three of 106 patients took more drug than prescribed.

3.7. Predictive value of i.v. testing

Dellemijn et al. (Dellemijn and Vanneste, 1997; Dellemijn et al., 1998) showed a significant positive correlation between pain relief during i.v. testing and open label follow-up of transdermal fentanyl, and claimed that it could predict non-responders better than good responders. In another study a significant correlation was observed between the analgesic effects of morphine during the injection and that observed 1 month after the oral titration (Attal et al., 2002), but only 20% of patients still had pain relief with oral morphine after 1 year. However, in a third study there was no predictive validity of i.v. morphine or placebo test infusion for subsequent pain reduction (Huse et al., 2001), though in only 12 patients.

4. Discussion

This review is based on data from 1145 patients with follow-up times of up to 8 weeks in controlled studies and up to 2 years in open follow-ups. Patients in most studies had previously used opioids. The design of trials was generally good, although not all important clinical issues

were addressed. For instance, functioning and quality of life were not evaluated in all studies and the methods were inconsistent. No firm conclusions could be made about concerns such as tolerance and addiction. Studies were small, affecting any conclusions based on this review. Open label follow-ups of controlled studies were included as they provided long-term data on adverse events, compliance and tolerance, however messy.

Opioids alleviate nociceptive and neuropathic pain (Fig. 2), but trials reported large individual variation. Three studies specifically assessed allodynia associated with neuropathic pain, and even dynamic allodynia was reduced by opioids (Attal et al., 2002; Rowbotham et al., 1991; Watson and Babul, 1998). There were no predictive factors for opioid sensitivity, implying that each patient needs to be individually tested with opioid.

The predictive value of intravenous opioid testing was good at identifying those patients who did not respond to opioids, i.e. those who had a poor response with the i.v. opioid test and also with either oral or transdermal opioid (Attal et al., 2002; Dellemijn and Vanneste, 1997; Dellemijn et al., 1998). I.v. doses of either morphine or fentanyl that were infused were about the maximum tolerated. It is unlikely that increasing the i.v. dose could have identified more positive responders. Oral or transdermal doses were usually lower, indicating that patients can manage only with lower doses in everyday life when uncompromised movement and cognitive function are needed.

Mean pain relief with opioid was about 30%. The lowest maximum doses, morphine 30 mg and oxycodone 20 mg daily, were used in musculoskeletal pain and were not effective. This is not surprising, as most of the patients had previously used equianalgesic doses of codeine. Adverse events prevented many patients from increasing the opioid dose to the maximum allowed to improve pain relief.

Substance abuse, psychosis or major depressive disorders were exclusion criteria in most studies. Dellemijn (Dellemijn and Vanneste, 1997; Dellemijn et al., 1998), however, showed that depressed patients could achieve significant pain relief with opioids. Opioids did not significantly improve depression scores in any study that assessed it, but mood improved with significant pain relief, as did quality of sleep.

Improved functional status seems to be a harder outcome as only three of eight studies found improvement in function or disability. Quality of life was improved in one of three studies assessing it. These measures, like mood, are affected by the amount of pain relief the patients achieve. It would be helpful to present information on numbers of responders and non-responders in addition to mean effects. That would provide information about what proportion of the patients can achieve meaningful pain relief with opioids and also what the consequences of this pain relief are.

Results for adverse events were obtained in studies with a form of enriched enrolment where dropouts before randomisation were mainly because of adverse events (Caldwell et al., 1999). Despite this, adverse events with opioids were common, with 80% of patients experiencing at least one. Constipation (41%), nausea (32%) and somnolence (29%) were the most common specific adverse events (Table 1) with numbers needed to harm of 3–5. After randomisation, more patients withdrew because of adverse events in the opioid treatment arm than with placebo.

In the clinic opioid tolerance is defined either as a decrease in pain relief when the opioid dose is stable or as a need to increase the dose in order to maintain pain relief. A 'honeymoon' effect of rising pain intensity after the first few weeks of good pain relief was seen in the study by Moulin et al. (1996), and also to some extent by Caldwell et al. (1999). Increased levels of pain intensity could reflect tolerance or the fact that the patients were initially more active, developing more pain. In future studies assessment of tolerance should include all these elements, i.e. changes in opioid dosing, pain intensity and activity.

Many important questions about addiction and outcome in patients with complicated problems remain unanswered. Anyone with addictive behaviour was excluded from these trials. These studies were not designed to address problems of addiction that is a more challenging target to study in chronic pain patients. The criteria for addictive behaviour are harder to define in the presence of pain.

The patient population of the trials in this review represents the 'ideal' patients for opioid treatment. A good example is the MONTAS study (Maier et al., 2002) where out of nearly 1000 screened patients only 5% were eventually included. The results may thus not reflect the reality in the clinic.

The results of the open-label follow-up studies can at best be only indicative, because they did not use the same methodological rigour as in the controlled studies. Analgesic efficacy was not assessed systematically, which weakens the data and analysis to detect possible development of tolerance. The results, however, imply that, only a minority of patients benefit from long-term opioid treatment, with only 44% still on treatment at the end of follow-up. The role of opioids in the treatment of chronic non-cancer pain needs to be further assessed. The current review did not compare different opioids. A recent systematic review concluded that there is insufficient evidence to show that one long-acting opioid was better than another (Chou et al., 2003).

The efficacy and safety of opioids as compared with the alternative treatments such as antidepressants and anticonvulsants would be of interest. However, addiction and drug diversion are special features of opioids and need to be addressed in specifically focused studies if opioids are to be considered in more vulnerable patient groups. Definitions for meaningful pain relief, tolerance, addictive or problematic behaviour are needed. The inclusion of genetic and endocrinological studies is needed to answer certain questions. Study designs other than randomised controlled trials may be more appropriate than RCTs because of their

greater relevance to clinical practice. If simpler follow-up studies are to be used standardisation of outcome measures is crucial. Several guidelines have recently been introduced (Kalso et al., 2003; The Pain Society, 2004). It would be important to evaluate the impact of the implementation of these guidelines on the outcome of opioid treatment in chronic pain.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2004.09.019.

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